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FEE TRANSMITTAL for FY 2003

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[X] Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 165.00

Complete If Known	
Application Number	09/800,103
Filing Date	03/06/01
First Named Inventor	Donoho
Examiner Name	R. Landsman
Group Art Unit	1647
Attorney Docket No.	LEX-0143-USA

METHOD OF PAYMENT *(check all that apply)*

[ ] Check [ ] Credit Card [ ] Money Order [ ] Other [ ] None

[X] Deposit Account

Deposit Account Number: 50-0892

Deposit Account Name: Lexicon Genetics Incorporated

The Commissioner is authorized to: *(check all that apply)*

[X] Charge fee(s) indicated below [X] Credit any overpayments

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims	-20**=		X	=	
Independent Claims	-3**=		X	=	
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	**Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840**	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBTOTAL (3) ($) 165.00

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	Lance K. Ishimoto	*Registration No. (Attorney/Agent)*	41,866	*Telephone*	(281) 863-3333
Signature	Lance K. Ishimoto by Peter G. Sefenan Reg No 40167			*Date*	October 23, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	Donoho *et al.*	Group Art Unit: 1647
Application No.:	09/800,103	Examiner: R. Landsman
Filed:	March 6, 2001	
Title:	Polynucleotides and Polypeptides encoding Human Transporter Proteins	Atty. Docket No. LEX-0143-USA

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

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APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed March 19, 2003. The Notice of Appeal was timely submitted on June 19, 2003, and was received in the Patent and Trademark Office ("the Office") on June 23, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of two months to and including October 23, 2003, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief (**$165.00**), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on March 6, 2001, claiming the benefit of U.S. Provisional Application Numbers 60/187,120 and 60/204, 725 which were filed on March 6, 2000, and May 16, 2000, respectively. As filed, the application included original claims 1-12. A Restriction and Election Requirement was issued by the Office on May 30, 2002 (Paper No. 9), in which the Examiner determined that the original claims represented into eight separate and distinct inventions. In the Response to the Restriction Requirement, submitted to the Office on June 26, 2002, Appellants elected, without traverse to prosecute the claims of the Group II (Claims 1-3) for prosecution on the merits. Appellants further elected, pursuant to 35 U.S.C. § 112, the species of SEQ ID NO: 1 for initial examination on merits. Therefore, claims 4-12 were cancelled without prejudice or disclaimer as being drawn to a non-elected invention. Appellants also added new claims 13-14 to better claim the present invention. A First Official Action, was issued on September 10, 2002 ("the First Action": Paper No.10), in which claims 1-3, 13-14 were rejected under 35 U.S.C. § 101, due to an alleged lack of patentable utility. Claim 4 was also rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. Claims 1-3, 13-14 were also rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and written description. Claim 2 was rejected under 35 U.S.C. § 112, second paragraph as being indefinite and claims 1,13 and 14 were rejected under 35 U.S.C. § 102(e) as being anticipated by Ruben et al., (WO 99/40100). In the response to the First Official Action, submitted to the Office on January 10, 2003 ("response to the First Action"), Appellants amended claims 1-3 to better claim the present invention, and traversed the rejections.

A Second and Final Official Action, was issued on May 19, 2003 (the "Final Action"), which maintained the rejection of claims 1-3, 13-14 under 35 U.S.C. § 101, due to an alleged lack of patentable utility and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. Rejections of claims 1-3, 13-14 under 35 U.S.C. § 112, first paragraph for lack of enablement and written description was withdrawn Rejection of Claim 2 under 35 U.S.C. § 112, second paragraph as being indefinite and claims 1,13 and

14 under 35 U.S.C. § 102(e) were also withdrawn. In a response to the Final Action, submitted on May 19, 2003 (Response to the Final Action"), Appellants again addressed the outstanding rejections of the pending claims with regards to the continuing rejection of claims 1-3, 13-14 under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph. An Advisory Action ("the Advisory Action") was mailed on June 5, 2003, maintaining the rejection of claims 1-3, 13-14 under 35 U.S.C. § 101, as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph, as one skilled in the art clearly would not know how to use the skilled invention. A Notice of Appeal was filed by Appellants on June 19, 2003. A copy of the appealed claims is included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

For the purposes of Appeal Appellants believe that no additional outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human sequences that encode a human transporter protein. Also disclosed is the tissue expression pattern of these sequences (page 3, Section 5). The specification details a number of uses for the presently claimed sequences, including the detection and diagnosis of human diseases such as, *inter alia*, obesity, high blood pressure, connective tissue disorders and infertility (specification at page 12, line 33). Additional uses for the sequences of the present invention described in the specification include assessing temporal and tissue specific gene expression patterns (specification at page 6, line 28-30), particularly using a high throughput "chip" format (specification at page 6 through page 9), mapping the sequences to a specific region of a human chromosome and identifying protein encoding regions (specification at page 3, lines 5-8), determining the genomic structure and in diagnostic assays(specification at page 11, lines 6-17), such as forensic analysis, human population biology and paternity determinations. Thus, Appellants have described sequences encoding a novel human transporter protein, a class of proteins which are well known to those of skill in the art and which have well accepted utility.

VI. ISSUES ON APPEAL

1. Do claims 1-3, 13-14 lack a patentable utility?

2. Are claims 1-3, 13-14 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-3, 13-14 Lack a Patentable Utility?

The Final Action rejected and the Advisory Action maintained the rejection of 1-3, 13-14 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility, this rejection was maintained in the Advisory Action.

Appellants respectfully disagree, as the presently claimed sequence was clearly identified as a transporter protein (see, at least, the title and specification Section 2) and the sequences are clearly identified as encoding transporter proteins that share structural similarity with mammalian sugar and sodium-dependent inorganic phosphate transporters. In addition the application identifies transporter proteins as integral membrane proteins that mediate or facilitate the passage of materials across the lipid bilayer and identifies the role of transporter proteins in the export of chemotherapeutics and thus their role in multiple drug resistance. Thus, the biological role of the presently claimed transporter protein is well defined, it facilitates the transport of materials, more specifically sugar and inorganic phosphates, across the lipid bilayer.

In the First Office Action, (Paper No: 11: page 4, lines 11-13) the Examiner indicated that the instant situation is "directly analogous to that addressed in Brenner v. Mason, 148 U.S.P.Q. 689

(Sus. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent". Appellants respectfully disagree with the assertion that this is a direct analogy. An activity, such as anticancer activity, is clearly distinct from a term that defines a molecules function, in the present invention, the term transporter. Transporters are well known to have the biological function of transporting molecules across membranes. In contrast a term of activity, such as anticancer activity, does not identify a specific function. There are many ways in which a compound can have anticancer activity, it can have one or more of specific functions, such as but not limited to the ability to inhibit enzymes involved in DNA synthesis or repair. It could even, for example increase the activity of a transporter thereby enhancing the ability of a drug to cross the cell membrane. Thus, it is Appellants belief that those of skill in the art would readily recognize that while some might use the terms activity and function interchangeably, that the term activity is also used in a broader sense, such as with the term anticancer activity as used in *Brenner v. Manson.*

The First Office Action (Paper No: 11) also stated on the last three lines of page 4 that "Sequence homology alone cannot be accepted in the absence of supporting evidence, because the relevant literature acknowledges that function cannot be based solely on structural similarity to a protein found in the sequence database." The Examiner has presented a series of examples, albeit exceptional examples, in support of this position. First the Examiner cites an article by Skolnick, *et al.* (Trends in Biotech *18*:34-39, 2000) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick, *et al.* concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly

assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Appellants' assertions.

The Examiner next cited Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable and directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. It should also be noted that in Table 1,on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Appellants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, " Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Appellants' assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement .

The action next cites Doerks *et al.* (Trends in Genetics *14*:248-250, 1998) in support that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Appellants point out

that transporters represent a well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Action's position against utility, Doerks *et al.* supports Appellants' position that the presently claimed sequences have a recognized substantial and credible utility.

The Examiner also cites Smith, *et al.* (Nature Biotechnology *15*:1222-1223, 1997) as teaching "that there are numerous cases in which proteins of very different functions are homologous" (Action at page 5). However, the Smith, *et al.* article also states "the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)" (page 1222, second column, first paragraph, emphasis added). Thus, Smith, *et al.* do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner next cites Brenner (Trends in Genetics *15*:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Appellants. Thus, the Brenner article also does not support the alleged lack of utility.

Finally, the Action finally cites Bork *et al.* (Trends in Genetics *12*:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted

that this article was published approximately 6 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination- the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure - function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 5 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes cleat that Bork et al. do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Appellants' assertions regarding the utility of the present invention.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention

underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1B.S. and 5 Ph.D. level scientists).

Furthermore, these articles are just examples of the few spurious articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. Appellants agree that there is not 100% consensus within the scientific community regarding prediction of protein function from homology information, and further agree that prediction of protein function from homology information is not 100% accurate. However, Appellants respectfully point out that the lack of 100% consensus on prediction of protein function from homology information is irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility, and that 100% accuracy of prediction of protein function from homology information is **not the standard** for patentability under 35 U.S.C. § 101. Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Appellants submit that the overwhelming majority of those of skill in the relevant art would **believe** prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools, as evidenced by extensive number of journal articles (which support Appellants' assertion that the overwhelming majority of those of skill in the art place a high value on prediction of protein function from homology information and the usefulness of bioinformatic predictions), and would thus **believe** that Appellants sequence is a transporter protein. As **believability** is the standard for meeting the utility requirement of 35 U.S.C. § 101, and **not** 100% consensus or 100% accuracy, Appellants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that

Appellants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

Additionally, to further support Appellants' position that those of skill in the art would find the assertion that the sequences of the present invention encode a transporter protein credible, is a compilation of the results of functional protein domain analyses using several of the available methods known to and accepted by those of skill in the art as **Exhibit A**.

InterPro (http://www.ebi.ac.uk/interpro/) is a publically database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences. InterPro analysis of SEQ ID NO:2 of the present invention clearly shows it to be, as Appellants have asserted, *a transporter protein.*

Pfam (http://www.sanger.ac.uk/Software/Pfam/index.shtml) is a large collection of multiple sequence alignments and hidden Markov models covering many common protein domains and families. For each family in Pfam you can: Look at multiple alignments; View protein domain architectures; Examine species distribution; Follow links to other databases; View known protein structures. Pfam analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, *a transporter protein.*

ProtComp analysis (http://www.hgmp.mrc.ac.uk/GenomeWeb/prot-anal.html)is used in Identifying sub-cellular location of a protein in animals and fungi. Results of a ProtComp analysis of SEQ ID NO:2 of the present invention shows it to be an integral membrane protein. Appellants have asserted that the sequences of the present invention encode a transporter protein, whose function is to mediate or facilitate the passage of materials across the lipid bilayer, thus logically those of skill in the art would recognize that *transporter proteins are often integral membrane proteins.*

SMART (a Simple Modular Architecture Research Tool: http://smart.embl-heidelberg.de/) analysis allows the identification and annotation of genetically mobile domains and the analysis of

domain architectures. More than 500 domain families found in signaling, extracellular and chromatin-associated proteins are detectable. These domains are extensively annotated with respect to phyletic distributions, functional class, tertiary structures and functionally important residues. Each domain found in a non-redundant protein database as well as search parameters and taxonomic information are stored in a relational database system. User interfaces to this database allow searches for proteins containing specific combinations of domains in defined taxa. SMART analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, *a transporter protein.*

TMHMM analysis (http://www.cbs.dtu.dk/services/TMHMM/) predicts transmembrane helices in proteins and TMHMM analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be an integral transmembrane protein, as those of skill in the art would expect of a *transporter protein.*

Finally, ProDom analysis (http://prodes.toulouse.inra.fr/prodom/2002.1/html/home.php) is a comprehensive set of protein domain families automatically generated from the SWISS-PROT and TrEMBL sequence databases. ProDom analysis of SEQ ID NO:2 of the present invention once again clearly shows it to be, as Appellants have asserted, *a transporter protein.*

In summary, all of the evidence presented as a result of analysis using a series of different methods recognized by those of skill in the art, clearly agree and identify the sequences of the present invention as encoding an integral membrane transporter protein, as Appellants have asserted. Therefore, clearly, Appellants' assertion that the sequences of the present invention encode a transporter protein are credible and would be accepted by those of skill in the art.

Given the historic legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Appellants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be

considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

Clearly evidence supports Appellants' assertions that the sequences of the present invention which encode a novel human transporter protein, transporter proteins have well established utility that is recognized by those of skill in the art. Thus the present situation parallels Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity to a protein having a known function. In the Analysis portion of Example 10 it states that "Based on applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO:2 encodes a DNA ligase . Further DNA ligases have a well-established use in the molecular biology art based on this class of proteins ability to ligate DNA. .....Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed..... Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made."

The present case is similar to that presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55). In the present case it is clear that the sequences of the present invention encode a transporter protein. Transporter proteins have a well-established utility. "Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed...Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made." Thus the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

Furthermore, the Advisory Action disregards Appellants' assertions regarding the use of the presently claimed polynucleotides on DNA gene chips, based on the position that such a use would

allegedly be generic. Further, these Actions seem to be requiring Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Appellants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications.

However, clearly given the utility described above for the transporter protein encoded by the sequences of the present invention, the claimed sequences provide a specific marker of the gene encoding the human transporter and provide a unique identifier (the sequence specifically identifies the gene) of the corresponding gene in the human genome. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing transporter gene expression using, for example, DNA chips, as the specification details at least on page 5, line 30 through page 6, line 33. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, exemplified by U.S. Patent Nos. 5,445,934 (**Exhibit B**), 5,556,752 (**Exhibit C**), 5,744,305 (**Exhibit D**), as well as more recently issued U.S. Patent Nos. 5,837,832 (**Exhibit E**), 6,156,501 (**Exhibit F**) and 6,261,776 (**Exhibit G**).

The Board is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such DNA gene chips, such as the presently claimed sequences encoding a human transporter must in themselves be useful. Moreover, the presently described transporter provides uniquely specific sequence resources for identifying and

quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

The utility of the sequences of the present invention are further enhanced by the description in the specification of tissues expressing the sequences of the present invention (Page 3, Section 5) These teachings along with the above evidence that the molecules of the present invention encode a transporter protein of known function, clearly demonstrates the outstanding utility of the sequences of the present invention in DNA chip expression analysis.

Still further, as only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Additional evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically

human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304; **Exhibit H**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153; **Exhibit I**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Given the physiologic activity and importance of transporter proteins as known to those of skill in the art, those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the described proteins. The use of the claimed polypeptide in an array for screening purposes Appellants respectfully point out that nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequence has been identified, as have tissues of interest, as in the present case. Once the role of the particular nucleic acid is known, the level of gene expression has and even greater significance. By identifying the physiological activity role of the claimed sequence, the claimed sequence has a far greater utility in gene chip applications that just any random piece of DNA. Appellants respectfully submit that **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, is distinct from the requirement for a **unique** utility, which is clearly an improper standard. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Therefore, just because other nucleic acid sequences find utility in gene chip applications does not mean that the use of Appellants' sequence in gene chip applications is not a specific utility. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office.

If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome (specification at page 11, lines 6-17), for example mapping the protein encoding regions as described in the specification (specification at page 3, lines 5-8) and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily

appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence supporting the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Appellants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit J**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 13 exons spread non-contiguously along a region of human chromosome 20, more specifically 20q at approximately 62.25-62.4M bp, which are contained within clone AL121673.41. Thus clearly one would not simply be able to identify the13 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were. The determination of the number of exons has been made

and that this does not represent empirical data. Appellants respectfully disagree and note that those of skill in the art would readily recognize that when a sequence encoding an expressed gene is mapped onto know genomic sequence, that those area in which the sequence is non-contiguously mapped represent exon/intron boundaries and that the presence of an exon/intron boundary represents either the beginning or the end of an exon and thus the number of discontinuous genomic sequence (exons) that are linked (spliced) during expression, represents the number of exons encoding the expressed protein encoding sequence. Clearly this provided empirical evidence supporting Appellants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome that encodes the transporter of the present invention as well as the ability of such sequences to be used to identify functionally active intron/exon splice junctions.

Appellants respectfully submit that the question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the

assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art.

In re Angstadt and Griffin, supra; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Finally, with regards to the issue of due process, while Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479 (**Exhibit K**), 5,654,173 (**Exhibit L**), and 5,552,281 (**Exhibit M**; each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (**Exhibit N**; which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Given the rapid pace of development in the biotechnology arts, it is difficult for the Appellants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could

somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Appellants' invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

Thus in summary, Appellants have described novel nucleic and amino acid sequences that encode a novel human transporter protein and their tissue specific expression pattern. Furthermore, the sequences of the present invention encode the human transporter, a protein of well recognized function. The present situation is similar to Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when the full length sequence of the invention encodes a protein that has a well known function. Furthermore, Appellants have described a series of additional substantial, specific, credible and well-established utilities for the present invention. Therefore, Appellants submit that as the presently claimed sequence molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of the claims under 35 U.S.C. § 101 has been overcome. Thus, Appellants respectfully request that the rejection be overruled.

B. Are Claims 4, 11 and 12 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-3, 13 -14 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in **Section VIII(A)** concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*,

439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-3, 13 -14 have been shown to have "a specific, substantial, and credible utility", as detailed in **Section VIII(A)** above, the present rejection of claims 1-3, 13 -14 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-3, 13 -14 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence of SEQ ID NO: 2; and

(b) hybridizes under highly stringent conditions including washing in 0.1xSSC/0.1% SDS at 68°C to the nucleotide sequence of SEQ ID NO:1 or the full complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence of SEQ ID NO: 2.

13. A recombinant expression vector comprising the isolated nucleic acid molecule of claim 1.

14. A host cell comprising the recombinant expression vector of claim 13.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-3, 13-14 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

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Date

Lance K. Ishimoto Reg. No. 41,866
Agent For Appellants

LEXICON GENETICS INCORPORATED
(281) 863-3399

Customer # 24231